

Physiologic mechanisms underlying the failure of the “shock index” as a tool for accurate assessment of patient status during progressive simulated hemorrhage

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BACKGROUND:

Shock index (SI), the ratio of heart rate (HR) to systolic arterial pressure (SAP), is a metric often used to diagnose patients at risk of impending cardiovascular instability and hemorrhagic shock. We hypothesized that if SI reflected impending cardiovascular instability and shock in an individual, then: (1) elevations in SI and HR would be greater in individuals with low tolerance (LT) to progressive lower-body negative-pressure (LBNP) compared with individuals with high tolerance (HT), and (2) LT would be associated with greater vagal withdrawal of the baroreflex sensitivity (BRS) compared with HT.

METHODS:

A total of 187 healthy subjects (HT, 125; LT, 62) underwent exposure to LBNP until a SAP of less than 80 mm Hg (instability) was achieved. HR and SAP were used to calculate SI, and BRS was determined from spontaneous fluctuations in R-R interval and diastolic arterial pressure. Maximal cardiac vagal withdrawal was calculated as the difference between BRS at baseline and BRS at 100% LBNP tolerance.

RESULTS:

Contrary to our hypothesis, SI at 60%, 80%, and 100% LBNP tolerance in LT (0.59 ± 0.03 , 0.73 ± 0.04 , and 0.97 ± 0.06 , respectively) was lower ($p \leq 0.002$) than SI in HT subjects at the same levels (0.66 ± 0.03 , 0.84 ± 0.04 , and 1.24 ± 0.06 , respectively). Maximal cardiac vagal withdrawal was less ($p = 0.045$) in LT subjects (11.3 ± 2.2 ms/mm Hg) compared with HT subjects (14.9 ± 2.5 ms/mm Hg). The sensitivity of SI in identifying impending instability (SI, 0.9) at 80% and 100% LBNP tolerance was 13% and 63% in LT subjects and 34% and 91% in HT subjects, respectively.

CONCLUSION:

The low sensitivity of the SI observed in LT individuals is associated with a lower capacity to withdraw cardiac vagal activity and can lead to an undertriage of those patients most likely to develop early hemorrhagic shock. (*J Trauma Acute Care Surg.* 2013;75: S197–S202. Copyright © 2013 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE:

Diagnostic study, level II.

KEY WORDS:

Shock index; lower-body negative pressure; cardiac vagal withdrawal; baroreflex sensitivity; vital signs.

The ability to provide accurate and early identification by emergency medical personnel of patients at high risk for developing circulatory shock has been traditionally dependent on the availability of “legacy” diagnostic markers such as heart rate (HR) and systolic arterial pressure (SAP). Since stand-alone measurements of HR and SAP may prove to be insensitive or nonspecific for assessing unstable cardiovascular function,¹ clinicians frequently rely on the shock index (SI), or the ratio of HR to SAP, as a more sensitive indicator of patient stability.² In healthy adults, the SI score typically ranges from 0.5 to 0.7,³ with a score of greater than 0.9 being associated with a twofold risk for requiring massive transfusion⁴ and worse clinical outcomes.^{5,6} SI values as high as 4.0 have been reported in a swine model of hemorrhage to reflect the severity

of shock.⁷ Although progressive increases in the SI can be used as one indicator of imminent hemorrhagic shock, the SI has not always shown a consistent sensitivity to predicting the onset of shock.^{8–10} Although data related to the assessment of SI as a triage tool have been generated from the clinical setting in patients with hemorrhage and trauma, we are unaware of any systematic experiments in which the physiology underlying the SI has been conducted during progressive reductions in central blood volume similar to hemorrhage in humans.

Lower-body negative-pressure (LBNP) is a unique physiologic model that has been adopted to progressively reduce central blood volume in human subjects in a manner that is safe and reproducible¹¹ and similar to that of hemorrhage.¹² Previous investigations using LBNP have revealed that subjects have varied tolerance to hypovolemia; approximately 65% to 70% of individuals display relatively high tolerance (HT) to reduced blood volume, while 30% to 35% display low tolerance (LT), with earlier onset of cardiovascular instability (i.e., syncope).¹³ As such, individuals with LT to blood volume reductions are at higher risk for early development of hemodynamic decompensation (e.g., initial decompensatory phase of shock). We used this unique human model to compare the response of the SI in HT and LT subjects during progressive reduction in central blood volume. This experimental approach also allowed the opportunity to assess cardiac baroreflex sensitivity (BRS) as an underlying mechanism for the HR response

Submitted: October 12, 2012, Revised: November 29, 2012, Accepted: March 20, 2013.

From the United Negro College Fund (K.S.), Fairfax, Virginia; and US Army Institute of Surgical Research (C.V.S., C.H.-L., V.A.C.), Fort Sam Houston, San Antonio, Texas.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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DOI: 10.1097/TA.0b013e31829b73aa

J Trauma Acute Care Surg.
Volume 75, Number 2, Supplement 2

Report Documentation Page

*Form Approved
OMB No. 0704-0188*

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1. REPORT DATE 01 AUG 2013	2. REPORT TYPE N/A	3. DATES COVERED -
4. TITLE AND SUBTITLE Physiologic mechanisms underlying the failure of the shock index as a tool for accurate assessment of patient status during progressive simulated hemorrhage		
5a. CONTRACT NUMBER		
5b. GRANT NUMBER		
5c. PROGRAM ELEMENT NUMBER		
6. AUTHOR(S) Schafer K., Van Sickle C., Hinojosa-Laborde C., Convertino V. A.,		
5d. PROJECT NUMBER		
5e. TASK NUMBER		
5f. WORK UNIT NUMBER		
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX		
8. PERFORMING ORGANIZATION REPORT NUMBER		
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)		
10. SPONSOR/MONITOR'S ACRONYM(S)		
11. SPONSOR/MONITOR'S REPORT NUMBER(S)		
12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release, distribution unlimited		
13. SUPPLEMENTARY NOTES		
14. ABSTRACT		
15. SUBJECT TERMS		
16. SECURITY CLASSIFICATION OF:		
a. REPORT unclassified	b. ABSTRACT unclassified	c. THIS PAGE unclassified
17. LIMITATION OF ABSTRACT UU		
18. NUMBER OF PAGES 6		
19a. NAME OF RESPONSIBLE PERSON		

that contributes to SI. We hypothesized that if the SI was a sensitive decision-support tool for the assessment of patient status during hemorrhage, then (1) HR and subsequently SI would be higher in LT subjects at any relative reduction in central blood volume, and (2) a higher HR in LT subjects would be associated with a larger reduction in BRS (i.e., greater cardiac vagal withdrawal).

PATIENTS AND METHODS

Subjects

This study was conducted at the US Army Institute of Surgical Research, Fort Sam Houston, Texas, in accordance with a protocol reviewed and approved by the institutional review boards of the Brooke Army Medical Center and the US Army Medical Research and Material Command. One hundred eighty-seven normotensive, nonsmoking healthy adult humans (male, 109; female, 78; mean \pm SD: age, 28 \pm 8 years; height, 173 \pm 10 cm; weight, 75 \pm 15 kg) participated in this study after a physical examination and an evaluation of their medical history was performed by a physician to verify their suitability as participants. Although the majority of our subjects were recruited from the civilian sector, approximately 20% were active-duty military. Female subjects were not pregnant as confirmed by a urine pregnancy test 1 hour before experimentation. Participants were instructed to maintain their sleeping habits and to avoid exercise, alcohol, and the use of autonomic stimulants such as prescription (e.g., antihistamines, decongestants) or nonprescription drugs (e.g., caffeine) for 24 hours before testing to minimize the risk of atypical cardiovascular responses from their use. In a preexperimentation briefing, subjects received both verbal and written descriptions of all procedures and risks associated with the experimental protocol and were made familiar with the laboratory. Each subject who agreed to participate gave written consent via an institutional review board-approved informed consent form.

LBNP Protocol

Subjects were in a supine position within an LBNP chamber made airtight by a neoprene skirt sealed at the level of the iliac crest. Each subject was instrumented with electrodes in using a standard lead II electrocardiography (ECG) configuration for measurement of HR, and beat-to-beat finger SAP and diastolic arterial pressure were recorded by infrared finger photoplethysmography (Finometer Blood Pressure Monitor, TNO-TPD Biomedical Instrumentation, Amsterdam, the Netherlands).

The LBNP protocol consisted of a 5-minute controlled rest period (baseline) followed by 5 minutes of chamber decompression at -15, -30, -45, and -60 mm Hg, with additional increments of -10 mm Hg every 5 minutes until the onset of hemodynamic decompensation. The onset of hemodynamic decompensation and consequential termination of LBNP was identified with a combination of two criteria: (1) continuous decline of SAP of 100 mm Hg or less (95% in both LT and HT groups; 84% \leq 90 mm Hg in both groups); and (2) voluntary termination by the subject owing to the appearance of presyncopal symptoms such as dizziness, impaired vision, nausea, sweating, or malaise. On rare occasions, sudden

bradycardia occurred. In all subjects, reduced SAP preceded presyncopal symptoms. Subjects who expressed symptoms in the absence of reductions in SAP were not considered to have reached their 100% LBNP tolerance and were excluded from the study. Termination of LBNP was followed by a 10-minute recovery period.

LBNP Tolerance

Subjects were classified as either HT or LT to reductions in blood volume based on the LBNP level at which the experiment was terminated as a result of hemodynamic decompensation. Individuals have been characterized as LT and HT based on their performance to an orthostatic test such as standing (e.g., fainters vs. nonfainters). Based on similar HR responses in a population of nearly 95 males and females, there is evidence that the hemodynamic challenge to standing is near that of approximately -50 mm Hg LBNP.¹⁴ As such, subjects with LBNP termination at levels -60 mm Hg or lower were categorized as LT, while subjects who completed the level of LBNP at 60 mm Hg were categorized as HT.^{13,15-17}

Data Analysis

During LBNP protocol, continuous ECG and arterial pressure wave form signals were sampled at 500 Hz and digitally recorded using data acquisition software (WinDaq, DATAQ Instruments, Akron, OH). ECG signals were confirmed free of noise, arrhythmias, or ectopic beats by visual inspection and used to calculate R-R interval. Automated computer analysis was used to search the data record for sequences of three or more progressively decreasing systolic pressures with at least a 1-mm Hg change per beat and associated R-R intervals with at least a 4-millisecond change per beat.¹⁸ Cardiac BRS or gain was estimated with linear regression analysis using decreasing systolic pressures and R-R intervals. SI and BRS were analyzed during the final 3 minutes of each completed LBNP level using commercially available software (WinCPRS, Absolute Aliens, Turku, Finland).

For comparison between LT and HT groups, LBNP tolerance was normalized to the maximum level of LBNP attained by each subject, which was equivalent to 100% LBNP tolerance. For statistical comparisons, subtolerance LBNP levels were calculated to averages nearest to 20%, 40%, 60%, and 80%. In actuality, these levels were equal to 20% \pm 2%, 42% \pm 4%, 61% \pm 4%, and 80% \pm 5% for the HT group and 19% \pm 11%, 39% \pm 3%, 53% \pm 6%, and 75% \pm 2% for the LT group. All calculated average subtolerance values for LBNP were statistically similar (e.g., 20% for HT vs. 19% for LT) between HT and LT groups. SI and BRS were compared at multiple LBNP tolerance levels between 0% (baseline) and 100%. Maximum cardiac vagal withdrawal was calculated as the difference between BRS at baseline (0% LBNP tolerance) and BRS at 100% LBNP tolerance. Sensitivity refers to the ability of a metric to correctly identify a condition. We evaluated the sensitivity of the SI value of 0.9 to correctly identify impending cardiovascular instability at 80% LBNP tolerance when all subjects are within minutes of decompensation and at 100% LBNP tolerance when all subjects are at the point of decompensation.

Comparison of SI, BRS, and maximum cardiac vagal withdrawal between HT and LT subjects was analyzed by two-way

analysis of variance with repeated measures at calculated relative LBNP levels that approximated 0%, 20%, 40%, 60%, 80%, and 100% LBNP tolerance. Demographics were evaluated by unpaired *t* test using commercially available software (SigmaStat, Systat Software, Richmond, CA). Unless otherwise stated, all data are expressed as mean \pm 95% confidence interval (CI).

RESULTS

Subjects

Of the 187 subjects, LBNP was terminated at -30 mm Hg in 5 subjects, -45 mm Hg in 10 subjects, -60 mm Hg in 47 subjects, -70 mm Hg in 57 subjects, -80 mm Hg in 47 subjects, -90 mm Hg in 18 subjects, and -100 mm Hg in 3 subjects. Consequently, 125 subjects (66.8%) were classified as HT, and 62 subjects (33.2%) were classified as LT. Demographic and hemodynamic variables of both groups are presented in Table 1. While baseline HR was similar for both groups, presyncopal HR was significantly lower in LT subjects than HT subjects ($p < 0.001$). Systolic blood pressure (SBP) at baseline and presyncope was not different between groups, and 95% of subjects in both LT and HT groups experienced reduced SBP of less than 100 mm Hg before the onset of symptoms.

SI and Percentage of LBNP Tolerance

SI increased incrementally with decreasing central blood volume (progressive LBNP) for both HT and LT subjects (Fig. 1). LT and HT groups showed similar SI scores ($p = 0.539$) at baseline and the first two levels of LBNP (0%, approximately 20%, and approximately 40% LBNP tolerance). LT subjects exhibited lower SI compared with HT subjects at estimated 60% (LT, 0.59 ± 0.03 ; HT, 0.66 ± 0.03 ; $p = 0.041$), estimated 80% (LT, 0.73 ± 0.04 ; HT, 0.84 ± 0.04 ; $p = 0.002$), and 100% LBNP tolerance (LT, 0.97 ± 0.06 ; HT, 1.24 ± 0.06 ; $p < 0.001$). Average SI for both groups remained less than 0.9 through 80% LBNP tolerance in both LT and HT subjects.

SI and BRS

SI and BRS at three levels of LBNP (0%, 80%, and 100% LBNP tolerance) are shown in Figure 2. BRS decreased

TABLE 1. Demographics and Hemodynamic Variables of HT and LT Subjects

Demographics	HT	LT	<i>p</i>
n	125	62	—
Male	80 (64%)	29 (47%)	—
Female	45 (36%)	33 (53%)	—
Age, y	28 ± 8	28 ± 8	1.0
Height, cm	174 ± 10	172 ± 11	0.215
Weight, kg	76 ± 14	73 ± 17	0.201
Baseline HR, beats/min	64 ± 11	67 ± 9	0.083
Baseline SAP, mm Hg	131 ± 11	131 ± 11	0.896
Presyncopal HR, beats/min	118 ± 23	95 ± 20	<0.001
Minimum presyncopal SAP, mm Hg	73 ± 18	77 ± 12	0.115
Tolerance time, s	$1,869 \pm 262$	$1,323 \pm 252$	<0.001

"Presyncopal" refers to final values at the maximum level of LBNP tolerance.

Data are expressed as mean \pm SD.

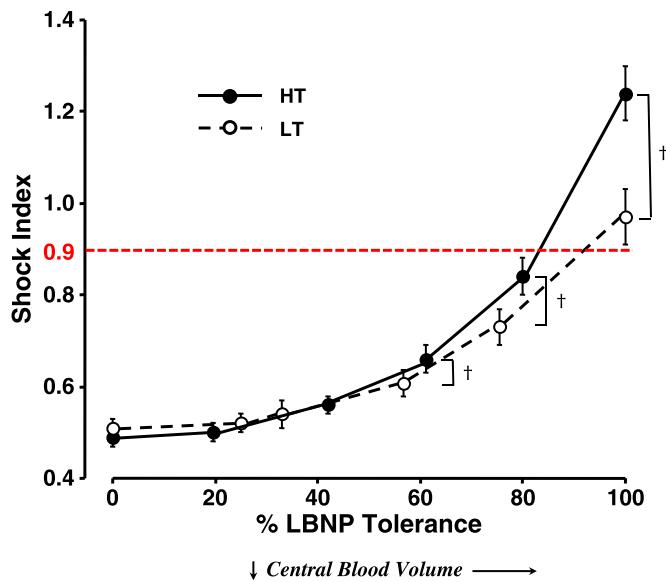


Figure 1. Relationship between the relative (%) level of LBNP tolerance (progressive reduction in central blood volume) versus SI. Data are expressed as mean \pm 95% CI. †Differences ($p \leq 0.002$) between LT (open circles and broken lines) and HT (closed circles and solid lines) groups at similar relative LBNP levels approximating 0%, 80%, and 100%.

incrementally with decreasing central blood volume (progressive LBNP) for both HT and LT subjects. BRS was lower in LT compared with HT subjects at 0% (LT, 15.6 ± 2.3 ms/mm Hg; HT, 19.0 ± 1.8 ms/mm Hg; $p = 0.004$) and 80% LBNP tolerance (LT, 8.2 ± 1.3 ms/mm Hg; HT, 5.4 ± 0.6 ms/mm Hg; $p = 0.034$). The change in BRS from baseline to 100% LBNP tolerance (i.e., maximum cardiac vagal withdrawal) was less ($p = 0.045$) in subjects with LT (11.3 ± 2.2 ms/mm Hg) than with HT (14.9 ± 2.5 ms/mm Hg).

SI Sensitivity

The sensitivity of using SI of 0.9 as a marker for impending hemodynamic decompensation in LT subjects was 13% at 80% LBNP tolerance and 63% at 100% LBNP tolerance, while the sensitivity of SI of 0.9 in HT subjects was 34% at 80% LBNP tolerance and 91% at 100% LBNP tolerance.

DISCUSSION

Since 85% of potentially survivable battlefield trauma deaths are attributed to hemorrhage¹⁹ and hemorrhage-related mortality drops to less than 4% once the patient has reached a hospital, the initiation of effective treatment in the prehospital environment is critical.²⁰ The SI has been proposed as a triage-assist tool to predict patient status in relationship to the risk of developing shock. The effective use of the SI as an indicator of "shock" is dependent on its ability to accurately identify hemodynamically unstable patients before the patient reaches levels of hypovolemia at which cardiovascular collapse occurs. In this regard, we used a human experimental model of progressive reduction in central blood volume that led to presyncope similar to that observed during hemorrhage and

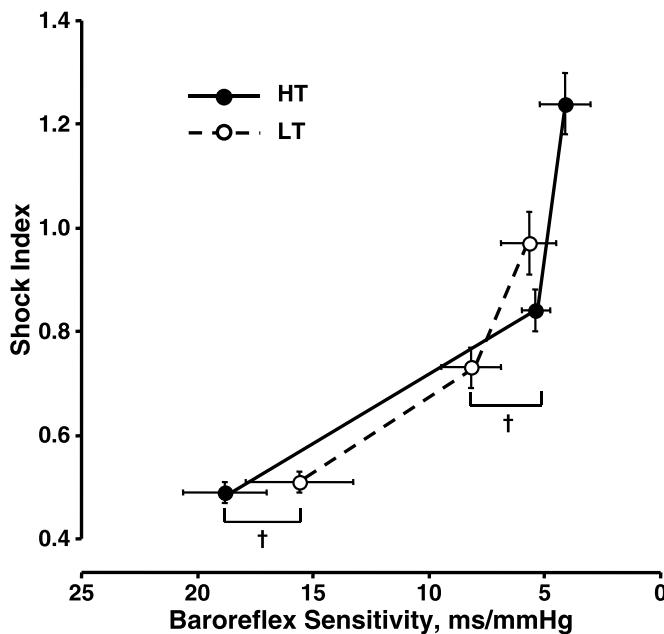


Figure 2. Relationship between the SI and cardiac BRS at progressive levels of percentage of LBNP tolerance (reduction in central blood volume). Data are expressed as mean \pm 95% CI. †Differences ($p \leq 0.004$) between LT (open circles and broken lines) and HT (closed circles and solid lines) groups at similar relative LBNP levels approximating 0%, 80%, and 100%.

measured the SI to test the hypothesis that individuals at high risk of developing an early onset of cardiovascular instability and decompensation (i.e., LT) would display a higher SI than those individuals with a stable hemodynamic condition (i.e., HT). Contrary to this hypothesis, we found that the SI was paradoxically lower in LT subjects at any relative reduction in central blood volume compared with that of the HT subjects. Although issues of inconsistent sensitivity in the use of the SI have been suggested based on uncontrolled clinical studies,^{1,8,9} we conducted the present investigation using a human experimental model that allowed us to systematically control the progressive loss of central blood volume to the point of cardiovascular decompensation. Our results are consistent with clinical reports in supporting the notion that the SI lacks sensitivity, particularly at low levels of central hypovolemia, in its capacity to identify impending hemodynamic instability in those individuals most at risk for early development of decompensation (e.g., early decompensatory phase of shock).

The use of HT and LT populations in the present investigation for testing the physiologic basis of the SI is founded on the premise that cardiovascular instability (decompensation) induced by LBNP does not reflect psychological responses in which LT subjects requested early termination before reaching 100% of their LBNP tolerance for concern about their well-being. If LT subjects were defined by terminating their exposure to LBNP before obtaining a “true” maximal tolerance, one might expect that SAP would not reach a hypotensive level until after symptoms were expressed. In contrast, the onset of hemodynamic decompensation and consequential termination of LBNP coincided with a decline of SAP of 100 mm Hg or less

before the onset of symptoms and voluntary termination in 95% of LT subjects as well as HT subjects. As reported previously,¹⁷ lowered perfusion pressure (SAP) coincides with significant reductions in mean cerebral artery blood flow velocity (i.e., lower cerebral perfusion) and the subsequent onset of symptoms. This physiology occurs earlier in LT subjects than in HT subjects.¹⁷ When cerebral artery blood flow velocity oscillations are maintained or reversed with inspiratory resistance, symptoms are delayed, and LBNP tolerance is extended.²¹ Taken together, these findings provide compelling evidence that the onset of symptoms in both LT and HT subjects are generated from inadequate cerebral perfusion (i.e., physiologic) rather than psychological mechanisms.

Overall, results of this investigation indicate that the utility of SI as an accurate indicator of central hypovolemia is limited. First, the SI predicted impending shock only very late in the progression of hypovolemia, as average SI scores in both LT and HT subjects remained below the clinically accepted threshold of 0.9 through 80% LBNP tolerance (Fig. 1). This suggests that SI is most sensitive as an indicator of central hypovolemia only in the very late stages of reduced central blood volume, although at this point, the individual (patient) has already entered the earliest stages of cardiovascular instability by which point it may be too late for effective intervention.^{20,22} Second, and contrary to our hypothesis, LT subjects had lower SI than HT subjects just before presyncope (60%, 80% LBNP) and at presyncope (100% LBNP tolerance) (Fig. 1). The SI of LT subjects at 100% LBNP (0.97 ± 0.06) was more comparable to the SI of HT subjects at 80% LBNP tolerance (0.84 ± 0.04) than at 100% LBNP tolerance (1.24 ± 0.06). Perhaps of greater note is that LT subjects at presyncope (cardiovascular instability) showed average SI scores only slightly above the 0.9 clinical standard for immediate intervention. When SI of 0.9 was used as a metric for identifying impending presyncope, the sensitivity of this metric was lower in LT than in HT at 80% LBNP tolerance (LT, 13%; HT, 34%) and 100% LBNP tolerance (LT, 63%; HT, 91%). This result indicates that more than one third of LT subjects (23 of 62 subjects) reached instability without ever displaying SI scores of 0.9 or greater. Therefore, an SI of 0.9 to identify impending cardiovascular collapse is not only a poor indicator of the early stages of hemorrhage but also an indicator with low sensitivity in individuals with LT to hypovolemia.

Our experimental design also provided the unique opportunity to investigate the contribution of baroreceptor control of HR on the SI response to central hypovolemia. The carotid-cardiac baroreflex functions to increase HR via myocardial vagal withdrawal during hypotensive stimuli such as those that occur during severe hemorrhage as a compensatory mechanism to maintain perfusion to the vital organs.²³ Individuals with relatively high baseline BRS display greater HR elevations for given reductions in SBP, a relationship that is associated with HT to hypovolemia.²⁴⁻²⁸ Our finding that baseline BRS was greater in HT subjects than in LT subjects is consistent with this relationship. Perhaps more important is the reserve to withdraw vagal activity during reductions in central blood volume, a phenomenon that is represented by the reduction in BRS from baseline to the point of maximal tolerance (100% LBNP).^{23,28} Thus, a lower reserve for cardiac vagal withdrawal of the

carotid-cardiac baroreflex can be associated with reduced elevation in HR although the SBP has dropped.²⁸ The findings of the present study are consistent with this notion that reduced elevation in HR through 80% LBNP tolerance was the primary cause for the lower SI observed in LT subjects and was associated with blunted cardiac vagal withdrawal as indicated by a smaller difference between baseline and maximal BRS compared with HT subjects.

Although a primary mechanism for elevated HR during blood volume loss is mediated through vagal withdrawal, the nonlinear characteristic of the BRS-SI stimulus-response relationship (Fig. 2) suggests that a sympathetically mediated mechanism also contributes to a late elevation in SI. Since the average vagally mediated BRS was altered very little ($p = 0.13$) between 80% and 100% LBNP tolerance in the face of significantly elevated SI for the HT subjects (Fig. 2), a mechanism associated with sympathetic nervous activation most likely contributed to the late tachycardia and abrupt increase in SI at the time of hemodynamic instability. Perhaps more important to the compensatory response is the observation that the average increase in SI was 65% greater ($p < 0.01$) in the HT compared with the LT subjects. These results suggest that a higher SI response in individuals who can tolerate a greater reduction in central blood volume is associated with greater compensatory reserve for both parasympathetic withdrawal and sympathetic activation of a cardiac chronotropic effect. This notion is consistent with previous observations that individuals with HT to reductions in central blood volume display greater vagal withdrawal and elevations in sympathetic nerve activity.²⁸

CONCLUSION

Based on our investigation, individuals who display LT to a reduction in central blood volume can represent one third of the general population. As such, our results infer that a significant proportion of trauma patients might possess diminished cardiac baroreflex responses that blunt their compensatory tachycardia during hemorrhage^{29,30} and consequently may be at risk of undertriage if caregivers rely on the SI as an indicator of hemorrhagic shock. Our findings provide the first data to describe the autonomic mechanisms that challenge the continued use of the “shock index” as a triage-assist tool because of its failure to identify those individuals at greatest risk of entering acute hemorrhagic shock.

AUTHORSHIP

All authors contributed to study implementation and writing of the manuscript. K.S. conducted the literature search and data analysis. She wrote the manuscript and produced the figures. K.S. and C.V.S. contributed to discussions about the study design and data interpretation. C.V.S. assisted with the literature searches and production of the figures. C.H.-L. and V.A.C. conducted the LBNP experiments, produced the database of results, and were responsible for the data interpretation. C.H.-L. supervised the data analysis and contributed to the writing of the manuscript. V.A.C. designed the study, conducted a critical review, and produced the final revision of the manuscript.

DISCLOSURE

This research was supported in part by funding from the US Army Medical Research and Materiel Command Combat Casualty Care Research Program.

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